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PART 15 HEARING - ADVERSE EVENT REPORTING TO IRBs
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MONDAY,
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The hearing was held at 9:00 a.m. in the Advisors and Staff Conference Room of the Food and Drug Administration, 5630 Fishers Lane, Rockville, Maryland, Dr. Janet Woodcock, FDA Acting Deputy Commissioner for Operations, presiding.

PANEL MEMBERS:
JANET WOODCOCK, M.D., Presiding Officer
KATE COOK, J.D., Office of Chief Counsel, FDA
SARA GOLDKIND, M.D., Office of the Commissioner, FDA
DAVID LEPAY, M.D., Ph.D., Office of the Commissioner, FDA
JOANNE LESS, Ph.D., Center for Devices and Radiological Health, FDA
PATRICIA ROHAN, M.D., Center for Biologics Evaluation and Research, FDA
BERNARD SCHWETZ, M.D., Office of the Secretary, HHS
ROBERT TEMPLE, M.D., Center for Drug Evaluation and Research, FDA

PRESENTERS:
THOMAS ADAMS, Association of Clinical Research Professionals
SANDRA L. ALFANO, Yale University
DAVID BORASKY, Applied Research Ethics National Association
GARY L. CHADWICK, Pharm. D., M.P.H., CIP, University of Rochester
PAUL COVINGTON, M.D., PPD
HOWARD B. DICKLER, M.D., Association of American Medical Colleges
MAUREEN DONAHUE HARDWICK, ESQ., Garner, Carton & Douglas
WILLIAM R. HENDEE, Ph.D., Medical College of Wisconsin
YVONNE HIGGINS, University of Pennsylvania
JUHANA IDÄNPÄÄN-HEIKKILÄ, Council for International Organizations of Medical Sciences
JOHN ISIDOR, Schulman Associates IRB, Inc.
GREG KOSKI, Massachusetts General Hospital
OWEN G. REESE, Jr., M.D., Western Institutional Review Board
JEAN-LOUIS SAILLOT, M.D., Schering-Plough
SORELL L. SCHWARTZ, Ph.D., Georgetown University Medical Center

WENDY STEPHENSON, M.D., M.S., M.P.H., Council for International Organizations of Medical Sciences
MICHAEL SUSKO, Citizens for Responsible Care and Research
VISH S. WATKINS, M.D., Eli Lilly and Company

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

9:11 a.m.

PRESIDING OFFICER WOODCOCK: Good morning. I'm Janet Woodcock, A cting Deputy Commissioner in the Food and Drug Administration. And I'll be serving as the Presiding Officer of the Hearing today.

On behalf of Acting Commissioner of the Food and Drug Administration, Lester Crawford, I'd like to welcome you to this publi c hearing on Reporting Adverse Events to IRBs.

With me on this panel are, from my right, Kate Cook, who is our Associate Chief Counsel at the Food and Drug Administration. Next to her is Dr. Sara Goldkind, our Bioethicist , who is in the Office of Pediatric Therapeutics at FDA.

Dr. Bob Temple, who is Director of Medical Policy at CDER, Dr. Joanne Less, who is the Associate Director for Clinical Research at CDRH, Dr. Patricia Rohan, who is Medical Officer in the Office of Vaccines at CBER -- sorry, I'm a little out of order here.

Dr. David Lepay, who is Director of the Office of Good Clinical Practice and Programs at the FDA, and Dr. Bern Schwetz, who is the Director

of the Office of Human Subject Protections at the U.S. Department of Health and Human Services.

Dr. Amy Patterson, who was going to join us from NIH, I understand is ill today and will not be with us. First, let me describe briefly the issues we're going to be talking about today and then the format we'll use for this meeting and is always used for this sort of meeting.

FDA is interested in hearing about the experience of IRBs, investigators, sponsors, data monitoring committees, and individuals who've participated in clinical studies concerning the reporting of adverse events to IRBs an d how the IRBs evaluate such reports.

We have heard that some institutions receive in excess of 12,000 adverse event reports a year to their IRB and that the clinical significance of these and relevance to the IRB function can vary considerably.

FDA re cognizes that the prevalence of large multi -center trials further contributes the volume of adverse events reported to the IRBs. To help us answer the questions that were posed in the *Federal Register*, we set up this public meeting to solicit the views of various stake holders,

investigators, IRB members, clinicians, professional trade groups, manufacturers, and consumers.

Here is how the meeting is organized to get that information. In the February 8th *Federal Register* we asked interested organizations and individuals to register to speak at today's meeting.

And we asked them to address three sets of questions. And those are laid out pretty clearly in the *Federal Register* announcement. Essentially, the first set of questions addresses the role of IRBs in the review of adverse event information from ongoing clinical trials.

The second set focuses on the types of adverse events about which IRB should receive information. And the third set of questions asked what approaches to providing adverse event information to IRBs could be taken to improve the current situation.

Nineteen people signed up today to help answer those questions. And we will hear from them first. When that is completed, and if time permits, we will open the floor to anyone else who wishes to address these questions.

If you are a scheduled speaker, we are requesting that you stay in the allotted time. And I will be assisting you in that task. Before we go on, let me stress that this is a listening exercise for the FDA.

We really want to hear what you have to say on these issues. We recognize this is very important for clinical research in the United States.

And we hope that important actions can come out of this meeting. We're going to have the meeting transcribed. And t he members of the panel and the staff at the FDA are going to pay careful attention to what they read in the transcript as we decide what to do about this issue.

This is not your last chance to comment. The docket will stay open until April 21 st. We're going to have a very busy day. So, let's begin with our first speaker.

What we'll do is each speaker will present in turn and then the panel may ask questions. We will not be taking questions from the floor today.

But we can have presentations at the end if time permits. Now, are first speaker is Dr.

Idänpään-Heikkilä, who is the Secretary General of the Council for International Organizations of Medical Sciences that we call here CIOMS.

And this organization has been working for three years, Dr. Idänpään-Heikkilä told me, in trying to address this problem. So, I look forward to hearing from you, please.

DR. IDÄNPÄÄN-HEIKKILÄ: Madam Chair, Good morning to everyone. I'm Juhana Idänpään-Heikkilä, and I function as the Secretary General of CIOMS. We are located at WHO in Geneva, Switzerland.

One slide, what is CIOMS? It's International, non -governmental, non -profit organization. And it was established more than 50 years ago by two UN organizations, UNESCO and WHO.

We are considered to be a fo rum to consider and prepare advice on consensus issues in research ethics and safety of pharmaceuticals. This morning I shall review some international documents, what they say about this issue.

And, in the end of my presentation I shall make a couple of proposals. And these are the major international documents I shall review. The first one is World Medical Association Declaration of Helsinki which, of course, is a

recommendation to any physician working in research.

But, as many of us know, Decl aration of Helsinki has become a guiding principal for almost all scientists doing clinical research, not only medical doctors.

The second document is European Union Clinical Trial Directive, which was issued in 2001 and became binding legal document for 25 countries in Europe, 25 countries who are members of European Union.

And that became binding from first of May, 2004. So, it has almost been for one year in force. And the third document is from my own organization, CIOMS International Ethical Guidelines on Biomedical Research Involving Human Subjects, which was updated in the year 2002.

And, to my knowledge, it's the only international ethical guideline so far. It's not binding. It's a recommendation. So, what do these documents say about the role of institutional review boards or independent ethics committees, as we tend to call them in Europe to emphasize their independence?

All these three documents agree that IRB

and independent ethics committee are responsible to protect safety and well being of subjects in clinical trials.

They also agree that the committees are required to monitor ongoing clinical trials. And the third point is that they all ask researchers to provide serious adverse events or reactions to IRBs and independent ethics committees.

So, what does this mean then? First, what European Union Clinical Trial Directive says. It states very clearly that the investigator shall report all serious adverse events immediately to the sponsor.

And the sponsor is responsible for the prompt notification to ethics committee. This is how the directive says. There is a guiding document which has basis on this directive, which defines suspected unexpected serious adverse reactions, SUSARs.

It's very European concept. And, this guiding document says that the sponsor should report fatal or life -threatening SUSARs as soon as possible, but not later than seven calendar days.

And follow -up information should be provided within eight calendar days. If one has

non-fatal, non-life-threatening SUSARs, they should be reported as soon as possible, but not later than 15 calendar days.

And it says that the CIOMS Form 1 should be used in reporting. Now, the guiding document goes a little bit further and says that independent ethics committ ees may only receive expedited individual reports of SUSARs as follows.

All SUSARs from member states and from third countries reported at least quarterly as a line listing accompanied by a brief report by the sponsor highlighting the main points for concern.

So, no single reports only, but also brief report by the sponsor highlighting the main points for concern. And it also says that any changes increasing the risk to subjects, any new issues affecting adversely the safety of subjects, not later than within 15 days.

It further says that sponsor is to submit once a year or on request a safety report with global analysis ethics committee taking into account all new available safety information received during the reporting, period.

Now, as Madam Cha ir mentioned, CIOMS set up, 2001, a working group which was addressing

whole issue, how to manage safety information from clinical trials.

But as a part of this, we were also considering the role of ethics committees and reporting safety to ethics commit tees. And the composition of this group is here.

We have regulatory authorities, EMEA, which is the European Medicines Evaluation Agency, we have the German Regulator, we have Health Canada, we have FDA.

We have Ministry of Health, Labor and Welfare o f Japan. We have the UK regulator, Swedish regulator, Australian regulator, and even from Argentina and Croatia people who were working with regulatory agencies, including also Morocco.

And, from pharmaceutical industry we had many, many leading multi -national companies listed here, Aventis, AstraZeneca, Bayer, Eisai/Japan, GlaxoSmithKline, Lilly, Merck & Company, Novartis, Pfizer, Roche and Wyeth.

And we sat down and we were considering carefully what to recommend. We soon noticed that individual cas e reports is not effective means of communicating important safety data.

You send them there, but it does not

really respond to the main point here because, how to put a case into perspective, investigators, IRBs, and international ethics committees lack resources to handle large volumes of reports.

These committees often operate on voluntary basis and lack time and expertise for analysis of cases. And we all agreed the current system is paper -intensive process and need for simplification is there.

So, what is our recommendation? We simply say, replace the current practice of sending large number of individual case reports to IRBs, international ethics committees with a more reasonable approach, periodic and adhoc communication to investigators and e thics committees that include regular updates of important safety information as well as a evolving benefit/risk profile and highlights important new safety information.

Significant new safety information, which sometimes means a single case report, that has implications for the conduct of the clinical trial or warrants an immediate revision to the informed consent would be communicated on expedited basis.

If I may close my presentation with my

own small example, if I was responsible for a two year study where I was studying pain medication, and everything went well, I would send in periodic safety reports.

But if then, say at month of 15, I suddenly had unexpected two myocardial infarctions, and maybe two strokes, I would immediately report these to the sponsor and to the regulatory agents.

I think this was my message. Thank you Madam Chair.

PRESIDING OFFICER WOODCOCK: Thank you very much. Don't run away, sir. Are there any questions from the panel? Yes?

MEMBER GOLDKIND: Could you give us a n example or two of what would be considered a suspected unexpected adverse event?

DR. IDÄNPÄÄN-HEIKKILÄ: Unexpected means that you don't have it in the investigator's brochure. Unexpected is that you just say, for heaven's sake, what is this? That's how I interpret this.

PRESIDING OFFICER WOODCOCK: Dr. Temple?

MEMBER TEMPLE: I was understanding you pretty good until you gave your last example.

PRESIDING OFFICER WOODCOCK: Nothing in

clarification.

MEMBER TEMPLE: You didn't say what the population was. But, what makes a heart attack or a stroke the sort of thing you would report as opposed to something that is very hard evaluate as a single episode?

My model for a single episode is hepatic necrosis, okay. But, how did that -- I mean, one might think that that raises the very problem that people are complaining about now, that people interpret unexpected conservatively and report everything, and thereby bury people.

What makes those examples seem so appropriate to you?

DR. IDÄNPÄÄN-HEIKKILÄ: I think the seriousness is very important.

MEMBER TEMPLE: Okay. So, they'd be obliged to report any death that occurred no matter what. Okay.

PRESIDING OFFICER WOODCOCK: Thank you. Dr. Lepay?

MEMBER LEPAY: Actually, two issues perhaps f or clarification, because I think it's important for understanding the European system. One is you use the term IRBs or ethics committees

are required to monitor ongoing clinical trials.

And it might be helpful if you could just say a few words about th at. I think our perspective relates more to continuing review on a relatively infrequent basis with exception of emergent events.

The other issue that I'd like to ask you about relates to the relative role in this process of the investigator and the spo nsor. Because you mention in one point that researchers should provide the information to ethics committees, but the recommendations both in the EU directive and from CIOMS seem to suggest that it's best that this come from the sponsor.

And I'm wonderin g if you see a role in this communication from sponsor to ethics committee involving some triaging, because this will come up again in other -- I think -- other presentations today.

DR. IDÄNPÄÄN-HEIKKILÄ: Yes, your first point was monitoring clinical tr ials, whatever monitoring means. To me they have the responsibility to protect the subject's in the clinical trial.

And that's a continuous responsibility.

It's not for our ethics committees to review the protocol prior to the trial. It has also responsibility to look after the trial.

I know that this does not take place in all European countries today. But this is the recommendation. I do not really get your point in the second question.

MEMBER LEPAY: let me just ask again, for a little further classification on that first point. Do you see that ethics committees have or should have a role?

I mean, there's a clear role to protect the rights and welfare of subjects. But, do you see that as necessarily meaning on a day -to-day basis following the clinical trial?

Is that what you mean by monitoring? Or is the role of the ethics committee, again, at some point to get summary information and to look at how to interpret that?

DR. IDÄNPÄÄN-HEIKKILÄ: Most of that, of course, comes from the repor ts and is not on daily basis. The ethics committees might get together once a month or every second week or whatever.

So, they cannot monitor on daily basis what is going on there. But mainly it is for the

reports and periodic reports, which I would emphasize in this context.

MEMBER LEPAY: And the second question really relates to the flow of information. I think, as you develop a recommendation from CIOMS, most of this has been phrased in terms of the sponsor being able to generate information, bei ng able to analyze this information.

Do you think that this information flow can occur from sponsor directly to ethics committee? Or do you believe there needs to be an intervening review triage by the clinical investigator between the sponsor and the e thics committee as a process issue?

DR. IDÄNPÄÄN-HEIKKILÄ: I would say ideally so that the investigator is involved in analysis and assessment of the situation. Just directly from the sponsor sounds to me a little bit odd because the investigator is st ill responsible for safety of those subjects who are in the trial.

In European countries, still in many of the European countries, the investigator is obliged to report all adverse reactions and adverse events to the public health authority.

It's a p art of the physician's

responsibility. So, not only to the sponsor, but to the public health authority. This means that in many European countries, the public health authority knows all that that the sponsor knows and knows also all that what is reported to ethics committees.

I think that is a kind of double assurance that we protect the patients who are a part of the clinical trial.

PRESIDING OFFICER WOODCOCK: Dr. Temple?

MEMBER TEMPLE: Yes, just to be sure I understand. The current EU directive that you cited seems to require a fair number of individual reports.

Is the CIOMS' recommendation for reducing that burden and spending more time on summarized material? That's what recommendation one seems to be saying without so many individual reports.

DR. IDÄNPÄÄN-HEIKKILÄ: Yes, this is --

MEMBER TEMPLE: Unless there's a significant report you gave an example of.

DR. IDÄNPÄÄN-HEIKKILÄ: Yes, as I said in the end of my presentation, you have a trial which say 1,500 patients and suddenly you have something unexpected, then you should react immediately to

that.

PRESIDING OFFICER WOODCOCK: Other questions from the panel? Joanne?

MEMBER LESS: Could you just elaborate a little more on the connection to the investigational driver device? I s there a suspected connection to the device or -- okay. Is there a suspected connection?

I mean, should it be reported whether there's -- is the suspected in connection to the investigational product in the sense that it could potentially be connected, probably connected, or they report it no matter what?

DR. IDÄNPÄÄN-HEIKKILÄ: This is, of course, a matter of taste that the investigator who has to decide, do I see any connection or not? And, if the investigator sees that there is a possibility that there is connection, I think this is enough to report it.

PRESIDING OFFICER WOODCOCK: Other questions? Okay. Thank you very much. That was extremely informative. Our next speaker will be Yvonne Higgins, who is the Associate Director for Human Research at the University of Pennsylvania.

MS. HIGGINS: Good morning. In a lot of

ways I feel like I've come home today because, for the past 20 years, I was actually a civil servant, federal civil servant, most recently working with Greg Koski and with Dr. Schwetz at the Office for Human Research Protections.

So, while my role here today is primarily to present the local review of one ground -level manager of an institution that has eight IRBs, I would also like to share with you my perspective from my previous role at OHRP.

During that time, I worked in the Division of Quality Assurances and was able -- had the good fortune of visiting over thirty institutions.

These were -- many of them were public academic institutions, private institutions. We visited six institutions internationally. We visited many community hospitals that were engaged in industry sponsored research.

And I'll tell you one thing, every time I opened up the discussion to a group of investigators, to a group of IRB members, to a group of IRB chairs, to the institutional official and I said, what is the pressing issue for you in this business of trying to protect human subjects,

almost always the answer was how in the world are we supposed to manage these adverse event reports that come to us individually from multi -center trials?

So, what I would do in my infinite wisdom as the Federal Regulator, is open up my dog -eared set of regulations and I would point to those things that I thought the IRB was supposed to do to determine that the risk benefit ratio continues to be acceptable, to determine whether the informed consent document requires revisions, and to determine whether subjects currently enrolled in this research need to be re-consented.

That is the role of the IRB in revie w of adverse event reports. Now, what I've just said is not novel. It's not my own idea. This has been supported by others, like Ernie Prentice and by a chorus of institutions who have just been trying to figure out how to deal with this information tha t comes individually as raw data.

So, after I had pulled out my regulations and clarified the role of the IRB in this process, I would then say, so, institution, investigator, IRB Chair, you need to go back to your industry sponsor, and you need to -- in my cheerleader way -

- push back against them and tell them you're not going to take this anymore.

You want meaningful data in the form of data safety and monitoring reports, in the form of summarized or aggregate data. You want some context.

You want some way of dealing with this. At a bare minimum, you want this stuff in some electronic form so you can throw it into a spreadsheet and make some sense of it.

And, usually at that point, they would start rolling their eyes, or twiddling their fingers because, in fact, they knew they couldn't push back as individuals.

Maybe collectively as institutions they could. But, as individual institutions or PIs, they could not push back. So, a year ago I went to the University of Pennsylvania and became the manager of the IRBs there, whose role is primarily to review biomedical research.

And, in that role, I decided that -- well, first of all, let me talk to you just about the shear weight of that role. Penn receives about 250 individual safety reports each week.

That's -- I think my arithmetic is

correct -- more than 13,000 from industry sponsors. And these come to us through the investigator in the form of a stack, usually about 15 or 20 inches high, with a letter on the top saying, please submit this to your IRB.

So, I went out and said to investigators and IRB administrators and IRB members, you don't really have to do this. And here is -- I got this note, I got an email from one of the investigators saying, okay, you said we don't have to do this.

But I want to read this cover letter to you from one of my industry sponsors. It says, quote, under the terms of the FDA Form 1572 and in accordance with the FDA Regulations Title 21 Code Federal Regulations, Section 312.32, there is an obligation to submit a copy of this IND safety report to your institution review board regardless of the protocol or the indication, or the context in which it's being studied, end quotes.

So, what are they supposed to do? What we've done -- so this -- actually, in this slide I just reinforce what I understand of the ethical and regulatory responsibilities of the IRB and the institution to review unanticipated problems that pose risk to subjects or others.

What we've done at Penn since I've been there, again, is not unique. This is a system that was developed by a number of institutions, including Washington University Medical College, Ernie Prentice at University of Nebraska, Gwen Okie at the City of Hope.

And it's one where we -- when we get these mounds of pap ers, individual IND safety reports, we immediately triage those into some way of making sense of them.

So, typically, I have each of my eight IRB administrators spend a good part of their day doing the initial triage to make sure that those reports that go to the Executive Chair for her review are ones that actually need to be considered.

The system that I'm going to suggest to you know was one that was reviewed Mike Carome at OHRP and endorsed informally by the office, and one that I would encourage FDA to consider.

And that is that the IRB should be provided with summary data for those events that are external to the institution, serious and expected, external serious, unexpected, and unrelated, external serious, unexpected and

possibly or definitely not related, and internal AEs that are not serious.

Instead, the IRB should be able to focus its attention on those internal adverse events that are serious regardless of expectedness or relatedness.

And I'll tell you the reason that we do that is bec ause we feel that, at our local institution we can go back to the PI and get information that's actually meaningful in order for us to interpret those SAEs and that we can actually have -- occasionally have some impact on deciding whether it was expected o r unexpected, related or not related.

And that the IRB should consider only those external events that are serious unexpected, and probably are definitely related, and that we welcome, urge, hope that industry sponsors would provide to us data safety and monitoring reports or some kind of meaningful information.

And those are the things that should be reported promptly to the IRB. So, at Penn, our interim solution is one that started about 1999 when Dr. Joe Sherwin became the Director of the Office of Regulatory Affairs.

And he set up a web -based system so that our individuals -- our investigators could provide to us in real time an electronically adverse event information that we could then print out, review, submit to the IRB if we needed to do, but also move into an Excel spreadsheet so that we could actually provide, gain some context for that information.

And this tool also allows the investigator to go in, capture these data, and print out reports so that they can meet their reporting obligations to their industry sponsors.

It looks sort of kind of like this. The investigator goes into the report, creates an AE record, and then that AE record is actually date - stamped so that becomes basis of the formal submission to the IRB.

The IRB Associa te Director then runs a report each day and submits to the executive chair of our IRB those reports that have been submitted through the system.

This may be hard -- I do not know if you can see this. But, it basically, even though the lay-out's different, it basically mirrors, I think, a MedWatch report or those other kinds of things where you're trying to capture those individual

data that you might need to collect to meet your regulatory responsibilities.

But I really see that as an interim solution to the growing problem of how to manage all these external events, although it has allowed us to get a handle on our internal events.

So, my recommendation , again joining the chorus of institutions who are hoping that we get some help from FDA in managin g these things, is that we'll get summary reports, DSMB reports.

And also, one thing I don't say here is that, at our institution, at the time of initial review, we often recommend to the investigator that they go back to the sponsor and ask for the spon sor to amend that section of the protocol that deals with monitoring.

Because, typically, that monitoring is limited to the sponsors monitoring for gate integrity, almost never includes how often safety reports are going to be submitted to the IRB through the investigator or how often a DSMB is going to meet, what are the stopping rules, how are those things going to be communicated through the investigator back to the IRB.

So, that's one way that we've been able

to handle those things at a local level. And you're looking at me like I need to stop, so I think I'll stop.

PRESIDING OFFICER WOODCOCK: Thank you very much. Are there questions from the panel?

MEMBER COOK: You mentioned the analysis that you're having your investigators do when they enter something into your web -based system, fill out the form.

Is it your experience that the investigators are able really to fill out the form completely? Do they generally have complete information about the events?

MS. HIGGINS: Most likely not at the time of the initial event. But then they can go back and build on that information and update it as that information becomes available. So, it's a very dynamic system.

MEMBER COOK: So, is this information only about events that occur in trials at University of Pennsylvania, or what about when they are notified about events that occur off-site?

MS. HIGGINS: We require our investigators to submit all internal SAEs through the system. We strongly urge them to use the

system to report those other events.

And we ask them not to report those ones that we don't need to see. But that just doesn't happen, as I said before.

PRESIDING OFFICER WOODCOCK: Dr. Temple?

MEMBER TEMPLE: If I understand your explanation of the problem, it is the combinati on of a rule that says unanticipated problems have to be reported to IRBs and the system that requires individual reports one -by-one within seven to 15 days of serious unexpected adverse reactions.

The sponsor, that is, has to report to all investigators such events. So that then sends them all on to the IRB.

MS. HIGGINS: We want to see those. We don't want to see those ones that have nothing to do with subject safety or nothing to do with events that will ultimately lead to a change in the protocol or a change in the informed consent document. And that's the ones that we would like to --

MEMBER TEMPLE: But here's my question.

MS. HIGGINS: Okay.

MEMBER TEMPLE: The things you'd like to report to the IRB are external adverse events

deemed by the sponsor or investigator to be serious unexpected, and probably or definitely related?

MS. HIGGINS: Yes.

MEMBER TEMPLE: And probably or definitely related is not the current standard. The current standard is associated with use of the drug, which is interpreted as possibly related.

That means Juhana's MI gets maybe reported as possibly, whereas most people wouldn't say it was definitely or probably. So, I want to know where you would like -- are you proposing a change in the reporting requirement for sponsors or a requirement that they classify them as possibly or probably, or what?

MS. HIGGINS: A classification would be great.

MEMBER TEMPLE: Now, don't you think they'd interpret them cautiously and call everything, you know, and report everything anyway and probably --

MS. HIGGINS: Well, isn't that the --

MEMBER TEMPLE: -- rank it as probably just so it gets to the IRB and it's covered?

MS. HIGGINS: I hadn't thought about it in those terms.

MEMBER TEMPLE: Okay. But, that is w hat you're proposing, a classification that is of the serious unexpected adverse reactions. You would like to see them classified so that only some of them would go on to the IRB.

MS. HIGGINS: What I want is clear guidance. I'm sorry about this. Dr. Lepay always asks for this. What I want is clear guidance at a Federal regulatory level that puts the responsibility for interpreting these things back on the sponsor and the investigator and allows the IRB to do its job of protecting human subjects.

MEMBER TEMPLE: Okay.

PRESIDING OFFICER WOODCOCK: Dr. Goldkind?

MEMBER GOLDKIND: I was wondering if you have any statistics given the 13,000 annual reports that you receive -- if they were restricted to serious and unexpected, what the figure would be.

MS. HIGGINS: Oh, I can provide you with those numbers. I didn't bring those with me. But, they are available.

MEMBER GOLDKIND: Okay.

MS. HIGGINS: I can tell you that our Executive Chair reviews probably -- ends up looking

at about half of the o nes that we get through the front door just because we as the IRB administrative staff can't really -- we have to go back to the investigator's brochure.

We have to go to the informed consent. And a lot of times there's still not enough information there for us to make a judgment. So, a lot of the possibly relateds, a lot of those other things end up going to the Executive Chair for her review.

And that often times means communication back and forth between our office through the investigator to the s ponsor. And it's a very cumbersome and time consuming process to get any information that helps us put it into context.

PRESIDING OFFICER WOODCOCK: Additional questions from the panel? Dr. Lepay?

MEMBER LEPAY: I just want a procedural clarification because, again, it varies a bit from institution to institution. Do you have procedures in place that require the investigator to effectively review all of the external reports that come into the institution and then triage before they go to the IRB?

MS. HIGGINS: We have a policy in place.

However, that involves a cultur al change that we have not been able to effect. So, in the end, we get the reports in big stacks.

MEMBER LEPAY: So basically, though, your internal procedure requires the investigat or to try to make sense out of these isolation reports --

MS. HIGGINS: Yes.

MEMBER LEPAY: -- and then make some determination.

MS. HIGGINS: But that's a recent change in our process. Before, I think, it was just -- as most institutions do -- you get them in, you give them to the IRB because you don't know what to do with them.

MEMBER LEPAY: How has that been -- and you may have already answered that in your previous remark. How has that been received by the investigators at Penn?

Are you g etting the same complaints that the IRB has otherwise --

MS. HIGGINS: Of course.

MEMBER LEPAY: -- articulated that they don't know what do with these reports either.

MS. HIGGINS: Absolutely. They cannot put them into any meaningful context.

MEMBER LEPAY: And, has the system at least --

MS. HIGGINS: Unless they've had the direct experience of having been involved in the adverse event. Although often -- I take that back because, usually, they are more subject matter experts than perhaps e ven the Executive Chair or the individual IRB members that review the report.

So, sometimes they add some meaning to those reports.

MEMBER LEPAY: And maybe I'm just reiterating the same question that Sara asked, but I'd just like to ask it in a slight ly different way.

The 13,000 reports each year that you review, how often, in fact, does that -- how many of those events, or how many of those reports lead to what you consider the purpose of IRB review, that is they've affected your risk benefit determination?

MS. HIGGINS: To a change in the consent for typically --

MEMBER LEPAY: A change in the consent or in terms of whether the subjects need to be re - consented?

MS. HIGGINS: I'm guessing no. But I would say a couple a week.

MEMBER LEPAY: A couple a week?

MS. HIGGINS: And, -- but more often it will result in a conversation between our office through the investigator and the sponsor to seek clarification about whether that really represents a risk.

MEMBER LEPAY: Okay. So you're saying probably up to about one percent of these actually -- because you're saying you get about 250 of these a week, give or take.

MS. HIGGINS: I'm guessing.

MEMBER LEPAY: Okay. Thanks.

PRESIDING OFFICER WOODCOCK: Additional questions form the panel? Dr. Temple?

MEMBER TEMPLE: I just had a follow -up on the last. Would those mostly be cases where the sponsor was proposing a change in the --

MS. HIGGINS: No.

MEMBER TEMPLE: -- consent or --

MS. HIGGINS: No.

MEMBER TEMPLE: -- where the --

MS. HIGGINS: Clearly where the sponsor proposes a change we do it. I'm talking about

cases in which -- you know, Vioxx is a good example of how, at Penn, it was -- Penn was one of the first institutions that noted the cardiovascular changes in -- as a result of Vioxx and required changes to the consent form as a result.

MEMBER TEMPLE: Based on individual reports or based on the --

MS. HIGGINS: Based on local -- primarily on local reports and careful analysis of those data.

PRESIDING OFFICER WOODCOCK: Any further questions? Yes, David?

MEMBER LEPAY: I'm sorry. I just wanted to also follow -up on the issue about data monitoring committee reports. One is whether you do receive these and secondly, how you or the IRB community as you know it has responded to these reports.

I mean, is it adequate to receive the open report from the data monitoring committee and for the IRB to use this as a basis of decision making?

MS. HIGGINS: We don't receive them routinely, even though we often asked f or them as a condition of approval in the protocol. When we do

get them, they sometimes help. And it's better than not getting them.

MEMBER LEPAY: Will the IRB rely on these if indeed they are receiving an open report -- excuse me a --

MS. HIGGINS: The IRB members at Penn really don't rely on anyone. They use that as additional data to make judgments about subject safeties.

MEMBER LEPAY: Thank you, that's all.

PRESIDING OFFICER WOODCOCK: Any further questions? Oh, one more. Dr. Less?

MEMBER LESS: I just was wondering, as you know, the requirements for device reporting are slightly different than drugs.

MS. HIGGINS: Right.

MEMBER LESS: And we've heard from some IRBs that they actually thing they're under-reporting device adverse events. And I was wondering, in your experience with your 250 a day whether you feel you're still getting flooded with device adverse reports or whether they're actually under-reporting those.

MS. HIGGINS: I do not see that.

MEMBER LESS: You don't see device

adverse --

MS. HIGGINS: Well, we see them. I do not see a flood of them.

MEMBER LESS: Okay. Thank you.

PRESIDING OFFICER WOODCOCK: Thank you very much. Our next speaker is Michael Susko, who is President of Citizens for Responsible Care and Research.

MR. SUSKO: Thank you. My name is Michael Susko. And I'm President of CIRCARE. We're the oldest organization where our prime objective is to look after the safety of human subjects.

And we'd like to talk about basically that, no matter what details we do, we have to keep in mind certain principals. And, unless we adhere to and keep them in focus, we will not be effective.

And so, I wanted to review those with you. The first is that we need to consider enactment of a national human subjects protections act that would cover all of research.

Currently, all that we're discussing today only impacts maybe 40 percent of the research. 60 percent is done by private industry

that has no mandated regulation.

And there are areas of gray z one where people aren't quite sure what is covered. So we should consider having all the protections here extend to all of research so that all humans can be protected.

With animals there is a welfare act or a safety act that all that research is perfec tly covered, but not with humans. So, let's keep that in mind as we go on.

The second major point is that there should be a national registry of adverse events reporting. Part of the confusion here is that we have each individual IRB setting up differe nt codes and not sure what the actual law is.

We need to have a national, uniform, clear standard that folks can follow. It looks like Penn has started to do a good job. They're setting up a web-based system.

And there's no reason in this age of modern technology why we can't have a web -based system that would be clear and uniform and so that we could analyze all the data and not be so confused.

So, it should be comprehensive. It

should be mandatory reporting, simple, and uniform, and perhaps even accessible by consumers. Good signs and good protection demands that we have accurate and uniform data reporting.

Perhaps it should be run by an independent agency. The first speaker was talking about levels of independent review. And that's a very important principal too.

So, who would run the national federal registry? Perhaps it should be outside of the FDA. The third principal is that we should always be attuned to the idea of managing and reducing conflicts of interest.

If you have an investi gator who is vested in a certain industry and they're being funded a certain way, there's not doubt they're going to -- it's going to affect the results somewhere.

It may even affect the adverse events reporting. So we want to manage and reduce, and control that to an extent. It can't be totally eliminated.

And it's going to be a factor. But, if we don't look at this issue, no matter what else we do, we won't be effective. The fourth principal is that we should have non -vested persons on various

levels of review that, whenever we do this, whenever we have committees and advisory bodies, if we're going to set up some review of the IRB, I mean, some outside source say, like what the first speaker was suggesting that it's not that adverse events are no t just reported to the investigator, but they're also reported to some public agency.

You need to think about putting in independent agencies or independent review with non-vested interested at various stages. It's used in other areas when there's probl ems, like air control safety, meat inspection.

It's not just the industry regulating itself. So, the important principal is to put non-vested persons. And, in terms of the IRBs, you want to have a percentage of those people who are just ordinary citizens and they don't have a vested interest in the outcome and the research and are likely to be more accurate in their reporting of adverse events.

So, what I'm suggesting is that we keep in mind the broad picture as we go through the details of what exactly are we going to report. We can always designate a committee and get the various parties together and actually hash out what

are the details.

But we need to keep in mind the major principals. The bottom line is, are human subject's going to be protec ted or not? And I would suggest that good science depends on the protection of human safety as well.

Because, if we have accurate reporting of adverse events, then we know we're getting good signs. We have to know when something doesn't work.

So that's good signs. But it's also good human subject safety. So, there shouldn't be a conflict of interest in there. So, I would just recommend in a simple way that we keep in mind those four principals, a national subjects protection act that would protec t all people in human research, a national registry of adverse event reporting so that we have uniform way across all the different IRBs in order to report the data and be consistent, that we always keep a mind to reducing and managing conflict of interest , and that we put non-vested persons on various levels of review as we go through this task of protecting human subjects. Thank you.

PRESIDING OFFICER WOODCOCK: Thank you

very much. Are there questions for this speaker from the panel? Dr. Goldkind?

MEMBER GOLDKIND: Your handout says that you think the FDA should give consideration to adopting the ICH standard definitions for adverse event reporting.

And I wanted to find out if you could expand on the ICH definitions that you think the FDA should adopt. It's on page three, at the top.

MR. SUSKO: Okay. I would have to refer that to a member of our -- you know, somebody more expert on that matter in terms of a specific comment.

PRESIDING OFFICER WOODCOCK: You can submit additional comments to our docket.

MR. SUSKO: Okay, thank you.

PRESIDING OFFICER WOODCOCK: Other questions? Dr. Temple?

MEMBER TEMPLE: I think I'm trying to understand the proposal. Most of the monitoring of adverse reactions and serious adverse reactions is sort of focused on the individual study, that is trying to see whether a drug is doing something bizarre so you can catch it right away and change the protocol or do something.

How does an overall system of adverse reactions that sort of folds all studies into it help you do that? I do not know, I'd be worried takes the focus away from the very thing you're most wanting to worry about. Can you elaborate on that a little?

MR. SUSKO: Well, I would think, aside from the local level, that you would want to see the pattern, you know, in different parts of the country and with different studies, like what's happening, you know, over a wider geographic zone in terms of the types of research that are done.

And some of these multi -study sites are in different areas . And they would need to be collated together. You'd have to have a uniform way of presenting that.

MEMBER TEMPLE: Well, I'm not sure. Again, I think the focus is, you know, the new drug that somebody's studying does something horrible to the liver.

MR. SUSKO: Right.

MEMBER TEMPLE: That's what you want to catch. I'm interested in your response. My worry would be that you'd lose that if you sort of captured everybody. These things tend to be

focused.

MR. SUSKO: Well, you wouldn't have to exclude a local reporting requirement. But it's just that you would need to have -- you know, we don't have a system that's accessible in a national level to see what's happening in terms of, you know, maybe similar studies that are being done and just the whole history of it, just accessibility, and a uniform way to analyze it so that we can see the patterns more clearly.

MEMBER TEMPLE: Perhaps you could compare studies of the same kind across different drugs conceivably, again.

MR. SUSKO: Right.

MEMBER TEMPLE: The other question about conflict of interest, my worry has always been about the involved investigator who, you know, really doesn't want to say anything bad happened to this wonderful drug he's working on.

MR. SUSKO: Right.

MEMBER TEMPLE: That kind of conflict of interest isn't resolved by anything. I mean, it's the report. It's observing the adverse reaction. That's the beginning of everything.

I just wondered if you had any thoughts

about that.

MR. SUSKO: You mean how to co ntrol for that?

MEMBER TEMPLE: Well, you know, some of the gene therapy issues arose as to whether the investigators were careful enough and so on.

MR. SUSKO: right.

MEMBER TEMPLE: That wasn't conflict by a sponsor. It wasn't conflict by an IRB. It was the very start of the whole process, namely the observation of something that may or may not be an adverse event.

That's the crucial beginning of all of this in some --

MR. SUSKO: You mean whether the researcher trying to make a new discover y sort of blinded to --

MEMBER TEMPLE: Yes.

MR. SUSKO: -- an ill effect. Yes, how you can --

MEMBER TEMPLE: I was wondering if you had thoughts about that.

MR. SUSKO: Yes, I do not know if you can control that sort of Nobel Prize type of --

MEMBER TEMPLE: Something like that.

MR. SUSKO: I just think you would have to -- that just presses the issue that the IRB or people looking in on the research would be independent of that, that their main objective would be to protect the human subj ect and not worried about, you know, well, is this going to be a great discovery?

So you just need to balance that out . I don't think you can fully control conflict of interest. There's always going to be some. It has to be managed and reduced.

PRESIDING OFFICER WOODCOCK: Other questions from the panel?

(No response.)

PRESIDING OFFICER WOODCOCK: No? Thank you very much. Our next speaker will be Dr. Sandra Alfano who is Vice Chair of Human Investigations Committee at Yale University.

DR. A LFANO: Thank you. Good morning. Thank you for this opportunity to address the questions from the FDA in a public forum. I have remarks that are somewhat different than what I had originally submitted.

IRBs have a primary responsibility to the subjects of research enrolled at a given site or

under the auspices of the local principal investigator or PI.

In regard to reporting adverse events, the role of the IRB goes beyond the review of individual adverse event reports. The role of the IRB is to ensure that there is an adequate plan in the individual study protocol for capturing adverse event data, submitting such data to the sponsor or data monitoring committee, DMC, for compilation or directly compiling the data in investigator initiated studies, for periodic assessment of such data, as in an interim analysis, for defining triggers or stopping rules that will dictate when some action is required, and for promptly reporting and un-anticipated problems to the IRB.

The detail and sophistication of such a plan will depend on the individual protocol features. What is the level of risk posed by the protocol?

What is the phase of the study? Is this a single-site or multi-centered protocol? Does an independent DMC exist? And is there blinding of intervention arms being used?

IRBs need to be attuned to unanticipated problems which may alter the risk benefit ratio of

an approved protocol, or may result in the need for change in the protocol procedures or consent form.

Thus, unanticipated problems that occur with an investigational agent are of interest regardless of site of occurrence. In addition, IRBs must ensure that local investigators in multi-centered trials are being adequately informed of new information that may affect the trial.

The local PI, which we view as the on-site expert in the trial intervention, should receive new information and assess it. Part of this assessment should involve decisions about whether the new information prompts a change in either study design, protocol procedures or informed consent.

If the PI believes a change is warranted, the information and amended protocol or consent form should be submitted promptly to the IRB for review and approval.

The current role of the IRB often seems like a warehouse for excessive reports that are burdensome. Rather than being provided with meaningful information that can information decisions, the IRB is inundated with many reports that simply cannot be interpreted for a variety of

reasons which I will discuss under question three.

The more appropriate role of the IRB should be in serving as an advisor to the local PI in assessment of important new information as the PI receives it.

So, regarding the types of adverse events about which IRBs should receive information, IRB s should be immediately informed if a serious, unanticipated event, thought to be related to the study protocol has taken place.

This is especially crucial if the event happened at the local site under the purview of the local PI. In such a case, the IR B has direct access to the investigative team.

And they work with the team to determine what, if any, additional information is required to do an adequate assessment. IRBs should work together with PIs to decide if changes are warranted by such an event.

The IRB retains the authority to require changes if necessary. While the IRB retains primary responsibility for on -site subjects of human research, important information can certainly come from other sites.

Thus serious unanticipated events that

happened at another site, or using the investigational agent under a different protocol may have relevance.

These reports should be sent by the sponsor to the local PI who should assess them and forward them to the local IRB if they are considered serious, unanticipated and related to the study agent in some way.

Anticipated events are known risks detailed in both the protocol and the consent form. If they occur , it is certainly not inconsequential or unimportant.

It is, however, simply unnecessary to spend time promptly reporting such known anticipated events to the IRB. Known site effects or adverse effects that occur as anticipated in the protocol and in practice will not prompt any action by the PI or the IRB.

And, as such, do not need to be repo rted. Anticipated events should not be reported to the IRB unless their frequency or magnitude exceeds expectations.

This requirement underscores the fact that all events need to be captured, collected, and compiled, and then periodically assessed to

ascertain whether something unexpected is occurring.

The responsibility for this activity rests with the sponsor and data monitoring committee if one exists. There may be circumstances when a thoughtful, local PI is prompted to make a change to the protocol or consent form based upon something other than a serious unexpected report.

In such a case, the event triggering the request for change -- which, of course, is an amendment -- should also be submitted to the IRB in support of the requested change.

And then, as to approach us to providing this information to IRBs, I would start by saying that data should not be confused with information. Information is data that is bestowed with meaning and utility.

Often the safety reports distributed by pharmaceutical sponsors represent little more than data sets that do not inform anyone. Also, it is important to note that immediate changes to protocols and consent forms should not be prompted by isolated adverse event reports.

This is especially the case when studies

involve blinding of the interventions. Adverse events occur locally or they may have happened at a different center participating in a multi -center trial.

Indeed, it is common that adverse events are reported from multiple countries, as multi - national trials are now very routine. It is important to note, however, that these off -site reports are often made without breaking the blind.

So, it is impossible to know which arm the subject was assigned to. And there is no ability for the local perso n forwarding the report to the IRB to get any additional information to allow an assessment.

These reports are seldom provided within any context. That is, there is seldom an analysis by the sponsor of the occurrence of similar events, nor an analysis of total number of subjects exposed to a given product.

Further, these external reports often involve uses in other disease states, different doses, and with or without concomitant medications. All of these factors serve to confound the analysis of a give n adverse event report and render the report rather meaningless.

It is generally agreed that a single report would not prompt action as it is being reported in such a large void. In contrast to this situation, the advent of protocol-specific monitoring committees, such as data and safety monitoring boards or data monitoring committees, referred to as DMCs, promises to offer an improved methodology for safety monitoring.

The sponsor or steering committee of a study constitutes the DMC and charges it to protect subject safety by examining the accruing data for indications that clear benefit or harm may be occurring.

The DMC then uses stopping rules to determine whether the trial should continue or not. The DMC usually looks at comprehensive data as investigators forward all adverse event reports to a data coordinating center, which then compiles the data for the DMC to review at pre-defined intervals.

Data presented to the DMC is either completely unblinded or characterized by treatment arm. As such, the DMC is able to determine whether a clear effect is being seen in one arm versus the other.

The DMC will then issue recommendations regarding the further conduct of the study based on this review. Thus, when a DMC exists, the recommendations from any meeting of the DMC must be submitted promptly to the IRB.

Recommendations to continue the study as planned assure the IRB that this level of review is taking place. Likewise, recommendations for change from the DMC will necessitate prompt action on the part of the local PI and IRB.

DMC oversight may not be an option in a number of studies. However, in the absence of a DMC, a sponsor's analysis of a given serious unanticipated event is mandatory.

The analysis must provide a context for assessment, i ncluding both number of similar events, as well as extent of exposure to the investigational agent, that is both numerator and denominator data.

The sponsor should make an assessment about the need for changes. And this then should be provided to the lo cal PI. The local PI should review the report and likewise make an assessment.

Or, for investigator-initiated protocols, the PI must provide the initial assessment. The

report with analysis and assessments should then be submitted to the IRB.

Adverse events that occur with investigational devices should follow the above recommendations. Again, it is necessary for the IRB to get input from the local PI in assessing any adverse device events.

Sponsor notification of the IRB directly circumvents this step and is undesirable. So, in summary, the role of the IRB is to ensure a good plan is in place for capturing adverse event data and recognizing when unanticipated problems are occurring.

Reporting to the IRB should be limited to these unanticipated o ccurrences in order to avoid over-burdening the review system and possibly missing important events.

IRBs should rely on DMCs to carry out their responsibilities. And IRBs should require reports from them. This is not a process that should be dictated by legalistic approaches, which may result in obscuring important information.

There are real dangers in basing decisions on incomplete or mis -information. The IRB needs to focus its energy and resources on

those important events that may require action . Thank you.

PRESIDING OFFICER WOODCOCK: Thank you very much. Are there questions from the panel? Dr. Temple?

MEMBER TEMPLE: I understand the preference for analyzed data and information that's useful. But, when you talked about what IRB should get with respect to individual reports, you appear to say that if they were local they definitely should be submitted.

This is for serious unexpected adverse reactions. If they were local they should be submitted because they'd have the wherewithal to pursue them.

But you also appeared to be saying that serious unanticipated events from another site also need to come to them. Now, that sounds like the current system.

So, I didn't see how continuing that fit with your preference for more useful data.

DR. ALFANO: I think there are two different systems. The current system may require serious and unanticipated events to be reported, but, indeed, what we receive go way beyond that.

We receive everything. Going back to your earlier question about --

MEMBER TEMPLE: Okay.

DR. ALFANO: -- conservatively assessing things. So, we -- I think many of us would be happy to only receive what we're supposed to receive.

Many people are under the impression that everything has to go to the IRB. But the second piece is, if a DMC does exist, then we believe you can rely on their more comprehensive and better look at unblinded data in place of submission to the local IRB.

MEMBER TEMPLE: On the first matter, do you think the problem is with the defini tion of what has to be reported or people's just terrified response that they report everything?

I mean, for example, the current definition means at least possibly related. That's how it roughly translates. Are you saying that should change to somethi ng more stringent like probably or perhaps some clarification that you shouldn't report silly things? Or what would you do about that?

DR. ALFANO: The biggest problem that I

see is people stop at the word serious. When something serious occurs they report it. And death is a great example.

It's pretty serious most of the time. But, very, very frequently it is not unanticipated. It's anticipated and not study-related. So, I think that we see a tremendous amount of reports that simply meet the criterion serious.

I understand your question about possible versus probable. Druthers would probably be for more probable and definite. But, I do not know that we could totally eliminate the possibles.

MEMBER TEMPLE: And, one last question. You and a number of people have remarked on how many of these individual reports are done without identifying the treatment.

DR. ALFANO: Yes.

MEMBER TEMPLE: Can you think of any reason not to identify the treatment? These people are all out of the study. And it's an isolated adverse effect.

Does that break the blind in some unacceptable way? Or would you think that usually they would be identified?

DR. ALFANO: Well, in practice, most

cases are not. And it's my understanding that the statisticians have pr oblems with breaking blinds will-nilly.

And so, they're applying their set of criteria to try to, you know, protect the data integrity.

PRESIDING OFFICER WOODCOCK: Additional questions? Dr. Lepay?

MEMBER LEPAY: You alluded to the issue of differen ces in reporting requirements between drugs and devices. I was wondering if you could just amplify a little bit on this, because obviously it's not just about FDA regulations.

There are other regulatory bodies involved in this process. And I'd be int erested in your perspectives on how much consistency and understanding of what the definitions are, as Dr. Temple has been alluding to, figures into this issue.

DR. ALFANO: Well, as you asked earlier, we do not receive a burden of reports on devices. So, whether device reports are being under -reported or not, I do not know.

We get a small number of device reports. But the problem our institution has instituted the

step of all the flow goes through the local PI to the IRB.

We do not accept reports fr om the sponsor to the IRB. We want the sponsor to notify the local investigator, and then the investigator to assess it and send it to us.

The regulation, as I understand it, for devices does require the sponsor to notify the IRB directly. And we find that problematic because we -- sometimes when we receive those reports we don't even know what protocol it's in relation to.

We have to do some digging because, of course, they use their own numbering system. We have our own numbering system. If they don't tell us who the PI is, it makes it onerous to even find what protocol they're referring to.

But, beyond that, we want to know what our local PI thinks about that report. And so, we believe that that should be changed, that it flow through the PI.

PRESIDING OFFICER WOODCOCK: Additional questions? Dr. Rohan, did you have a question?

MEMBER ROHAN: I think you basically answered it. I guess that was my question. In the last paragraph of your text you were sort of

talking about investigational devices.

And I just wondered how the sponsor reporting directly to the IRB, is that just an issue specifically to devices? Or do you see that with large multi-center trials as well?

DR. ALFANO: We occasionally would receive things directly from spons ors on multi - centered drug trials. We just send them right back to our local PI and ask that it be submitted properly.

So, I don't think that's terribly problematic. But I do think it's problematic with the devices.

PRESIDING OFFICER WOODCOCK: Dr. Less?

MEMBER LESS: Can I just follow -up on that? When a local PI sees an adverse event, they're supposed to report it to the sponsor and to the local IRB.

And, if they think it meets the definition of an unanticipated adverse event, the sponsor then c onducts an evaluation. So, what you get back from the sponsor shouldn't just be the report.

It should be their assessment and evaluation, and what needs to be done, if anything,

for the trial. And so, -- but you still think the local PI needs to weigh in on that again before it comes back from the sponsor in more detail?

I'm not clear at that point what the local PI -- because they've already told the sponsor what they think. They told you. The sponsor has done their assessment.

And then they're reporting back saying here's what we think should happen.

DR. ALFANO: What we receive from sponsors does not uniformly agree with what you've said. We do not always receive assessments.

MEMBER LESS: So you're getting just basically a report?

DR. ALFANO: Yes, number one. Number two, we infrequently receive any information that says whether anything should be changed.

MEMBER LESS: Okay.

DR. ALFANO: So, even if there is an assessment, some sponsors will attach pages and pages of like events and an analysis of that. Some sponsors do do that.

And the sponsors in the audience or people in the audience may think -- but we get many, many, many reports from sponsors that do not

have an analysis, regardless of the requirement, and do not say whether some change should happen.

MEMBER LESS: Okay. Thank you.

PRESIDING OFFICER WOODCOCK: Additional questions? Kate?

MEMBER COOK: Do you have any suggestions for specific actions you would like any of the agencies here to take in order to make what you've described come true?

DR. ALFANO: Well, I think at Yale we instituted a policy of requiring all data safety monitoring data, safety monitoring board or DMC recommendations be submitted to the IRB.

I think that that is a good requirement, that we can then rely on them having done their close review. The second piece -- and that's why I led off with it.

I believe that we should be looking at the -- I think my colleague from Penn talked about having the sponsors protocol better detail the monitoring that is planned, not necessarily just the monitoring of data collection and data integrity, but also the monitoring for adverse events.

And, again, at Yale we have instituted

that. All protocols submitted to Yale have to include a data safety monitoring plan that touches on how these events are going to be looked for, collected, compiled, and reported.

PRESIDING OFFICER WOODCOCK: Any other questions?

(No response.)

PRESIDING OFFICER WOODCOCK: Thank you very much. Our next speaker, a nd the final speaker before the break, will be Maureen Hardwick, who is a partner in Garner, Carton & Douglas and is speaking on behalf of the IRB Sponsor Roundtable.

MS. HARDWICK: Good morning. My name is Maureen Hardwick. And I'm a partner at the law firm of Garner, Carton & Douglas, which serves as the Secretariat for the IRB Sponsor Roundtable.

I'm pleased to speak today on behalf of the IRB Sponsor Roundtable and will provide some background of the Roundtable in a moment. The Roundtable comments FDA for organizing this hearing to begin gathering feedback from interested stakeholders on this critical issue of reporting adverse events to institutional review boards and multi-site trials.

The purpose of my presentation today is

to share the Roundtable's thoughts on possible best practices and potential new processes to improve reporting AEs to IRBs and multi-site studies.

This is a complex issue with many facets. And it is important to note that the Roundtable's views are under development and a re a work -in-progress.

The Roundtable intends to provide further input to FDA in the written submission invited in its 8 February *Federal Register* notice. After providing some background on the IRB Sponsor Roundtable, I will review the Roundtable's init ial feedback on the questions FDA raised in its public notice, particularly in the areas of IRBs' responsibilities and multi -site trials, the types of AEs that IRB should receive, how to enhance IRBs' ability to assess the implications of AEs for clinical study subjects, and the role of consolidated reports of AEs.

The IRB Sponsor Roundtable grew out of two forum meetings in 2003 that brought IRBs and pharmaceutical sponsors together to discuss important issues of HIPAA compliance in the clinical research context.

During these meetings, the two

communities engaged in a very productive dialogue. And there was a desire to continue this dialogue and extend it to other issues of common interest.

There was a consensus that IRBs' sponsors and the research enterprise in general will benefit from a neutral and constructive venue outside of individual protocols to address over -arching and recurring issues and that increased communication is appropriate and needed to enhance the protection of human research subjects.

The Roundtable is the first organization where sponsors and IRBs have come together as equal partners to address issues of mutual concern in a sustained and task-oriented manner.

The Roundtable's mission is to facilitate constructive communicatio ns between sponsors and IRBs on significant clinical research issues and, where possible, to propose practical strategies for improving clinical trial processes in human subject protections, and engage other effective stakeholders in the clinical research community to facilitate broader dialogue and consensus building.

This partnership makes a lot of sense and is long overdue. Both communities have profound responsibilities for protecting individuals

participating in clinical studies.

The Roundtable vi ews the current challenges associated with AE reporting as an extremely important issue to be addressed, and took this issue on as a priority from the outset.

The IRB Sponsor Roundtable was formerly organized in 2004 and is comprised of representatives f rom both communities. The Roundtable is still in a formative stage.

But we've had a strong core group engaged in getting it off the ground. The current participants are listed here. The Roundtable is independent from existing organizations.

And the goal is to have equal representation from both communities. As FDA has recognized, clinical studies are increasingly conducted at a large scale across numerous sites, both in the U.S. and around the world.

Frequently the sites are overseen by a different IRB. And each IRB receives individual represent of AE's experience and subjects enrolled in its own institution.

We refer to these as internal reports, as well as AE's experience by subjects enrolled at other institutions and perhaps other subjects f rom

entirely separate but related clinical trials.

These AE's that occurred in an institution other than the one that the IRB is directly responsible for we refer to as external AEs, as a number of speakers have this morning.

The shear number and disa ggregated nature of the reports make it difficult, particularly for IRBs, to effectively evaluate their significance and the implications for study subjects.

It is important to note that the existing regulatory framework was developed before multi - site t rials were commonplace. And the regulatory definitions and processes for AE reporting differ among FDA and other agencies.

Therefore, it is the Roundtable's view that the process would benefit from clear regulatory guidance relevant to multi -site trials. The next few slides review just a few of the relevant definitions, noting again that there are multiple definitions for adverse events or adverse experiences.

Frequently, when people speak of AEs, they're referring to the IND safety reports that are co mmunicated to FDA on an expedited basis for those events that are serious, unexpected, and

associated with the investigational drug.

Of course, there is also the term unanticipated problems involving risk to human subjects, which is perhaps broader than serious unexpected and associated, although significant overlap exists.

And there are also DSMBs and DMCs which are formal committees charged with monitoring safety during a clinical trial in providing recommendations to the study sponsor.

As they bega n considering possible solutions to the AE issue, the IRB and sponsor members of the Roundtable thought a great deal about what the goals of a new AE model should be.

And this slide highlights the primary overarching ones. First, to enhance the protecti on of human subjects by ensuring that medically relevant data on AEs is communicated to IRBs in a meaningful way, in particular highlighting those events that are more likely to alter the risk benefit relationship.

And to promote responsible and effectiv e AE reporting through a multi -party process that includes appropriate checks and balances and reinforces the active participation by all parties,

IRBs, principal investigators and sponsors, in identifying potential unanticipated problems.

Turning now to the IRBs' role in reviewing AEs in multi-site trials, and we will review this in more depth in our written submission, but wanted to highlight a few points today.

It is important to note that IRBs are not intended to function as safety oversight committees in multi-site trials and, indeed, do not have access to the type of relevant information necessary to evaluate large volumes of disaggregated external AE reports in order to put them into the proper context.

The substantial volume of data and the manner in which it is communicated have led to a situation where the signal-to-noise ratio is unfavorably dominated by noise for IRBs in attempting to review and analyze external AEs.

Therefore, it is the Roundtable's suggestion that the process for communicating external AE reports to IRBs should be a change to improve the situation.

The next several slides describe possible elements of a solution to this problem. I would

like to emphasize that this approach is not intended to keep information from the I RBs, but rather to ensure that the information flow makes sense and is structured in way to best promote the role in protecting human subjects.

So, review the core elements of the Roundtable's proposed solution. In the context of identifying unanticipat ed problems involving risk to human subjects, investigators should identify relevant external AE reports that require notification to the IRB.

Now, what is a relevant AE? It is a challenge. And the Roundtable realized this as we thought about this issue, to develop a detailed and comprehensive definition.

But the Roundtable proposes that the following criteria could be used to determine which external AEs should be sent to the IRB. First, any AE that would require modification of the study protocol or any AE that would require revisions to the informed consent form, or an AE that indicates some other major concern impacting the study.

This last criteria allows discretion depending on the needs and realities of a trial. It is important to note that under this model the

investigator's responsibility to submit all appropriate internal AEs to the IRBs would be unchanged and sponsors should continue to submit expedited AE reports to FDA pursuant to existing regulatory requirements.

It would be the spon sor's responsibility to clearly identify to the investigator all AE reports that meet the three criteria. And, as noted on the slide, this is already a best practice, as typically such reports would be singled out.

Three important points are noted on th is slide. Investigators should provide AE reports to IRBs that they believe meet the criteria for notification of IRBs even if the sponsor does not identify them as such.

If a principal investigator believes that an AE report not meeting the criteria sh ould be sent to the IRB, they should do so but provide justification for this transmission.

If the sponsor concludes that an external report warrants immediate referral to IRBs, it should highlight this to the investigators. In addition, the Roundtable proposes that some other best practices and checks and balances be

considered given the importance of appropriate safety monitoring in a study.

Sponsors and principal investigators should document their analyses of all external AEs so that this analysis and associated documentation would be subject to audit by the IRB or their designated compliance arm for the investigator site and by FDA for both sponsors and investigators.

Sponsors should, as part of the study protocol, also develop and justify a plan and schedule for communicating aggregate AE reports. This is an important point, so I'd like to discuss it a bit further.

This would be the means of providing on a periodic basis an aggregate summary of all external AE reports to the IRB so that, rathe r than getting them on an adhoc basis throughout the trial, the IRB would receive them in an orderly, coherent, and still timely fashion.

The protocols for many trials, for example, oncology studies, already contain detailed plans for how and when advers e events are reported. It is important that this communication plan be developed and implemented in a flexible manner to meet the specific needs of an individual clinical

trial.

Elements of the plan could include the proposed frequency for submission of aggregate safety information. This would likely often be quarterly, but could be semi -annually or annually, or some other timeframe if appropriate for the study, a proposed format for the submission of periodic qualitative assessment reports covering all safety information relevant to the trial, including all expedited AEs and other relevant safety information, and a description of the functioning of a DSMB if used for the study, and the method and frequency of communication of DSMB reviews to investigators and IRBs.

The Roundtable is grateful for the opportunity to participate in this hearing and to present its initial views on this important topic. The Roundtable encourages FDA to clearly articulate an official guidance best practices for reporting of external AEs and multi-site trials.

We will continue to discuss and further refine our thinking on this important topic. And, in particular, we will reflect on the presentations during this hearing today, consider the proposal recently issued by the CIOMS.

Based on our initial review, the CIOMS VI report appears consistent in many ways with the Roundtable's current thinking. And conduct outreach to other interested stakeholders, we believe is particularly important to obtain feedback from principal in vestigators given the central role they play in research and in the elements of the Roundtable's proposed model.

We will also continue to communicate with the interest of government agencies as appropriate and will submit written comments to FDA on this topic by the April 1st deadline. Thank you.

PRESIDING OFFICER WOODCOCK: Thank you. Are there questions from the panel? Yes, Dr. Rohan?

MEMBER ROHAN: Regarding the reporting of relevant external events, would you -- are you proposing just the report ing of these events, of the changes that the other IRBs at other sites made, the reasons they've made them?

You know, because sometimes an event may come to a particular IRB or a series of events, and then there are often discussions or communications with the investigators.

And then a decision is made. So, wasn't

sure if you implied that all that information would be also conveyed in association with the external adverse event reports.

MS. HARDWICK: It's a good question. We have not talked that mu ch in depth about what exactly would be reported other than the fact of the external report.

But I think we should do some thinking about that. Maybe in our written somebody we could address that.

PRESIDING OFFICER WOODCOCK: Additional questions? Dr. Lepay.

MEMBER LEPAY: I was just going to ask for just a bit of clarification. You seem to be focusing on maintaining a system for receiving appropriate internal adverse event reports.

But I'm not quite sure what you mean by all appropriate inte rnal AEs and what you define internal AEs as any AEs. So I was wondering if this is some subset, again, that you think needs to be focused in on, even internally.

MS. HARDWICK: Sure. When we talk about internal AEs, we are referring to the AEs for whi ch the IRB is directly responsible, for something occurring at their institution.

And the feedback that we had and the discussions within Roundtable were that those AEs should continue to be reported to the IRB as they, you know, as they are currently wi thout going through this sort of criteria triage system.

MEMBER LEPAY: When you say as currently, though, would you say from a regulatory standpoint those that are serious and unexpected or some broader categorization as well?

MS. HARDWICK: I think t he characterization we were looking at were unanticipated problems involving significant risk to human subjects.

PRESIDING OFFICER WOODCOCK: Dr. Temple?

MEMBER TEMPLE: It probably would be helpful if in your written further comment you address this s pecifically. But, the part about relevant external reports still seems unclear.

And I wonder if you could clarify that. As you know, the current standard is to report serious unexpected events sort of as they happen, even before you have any good ana lysis or before you have multiples of them.

So, ordinarily, the initial report won't lead to a study modification. It might come to

that later, or to revision for the informed consent might come to that later.

And other major concerns would be hard to say. So, it sounds to me like you're giving heavy responsibility to the investigator to take some of those reports and say, I'm not going to send those on to the IRB.

And my question is, are they going to be willing to do that, or will they just pass t hem all on as in the current system?

MS. HARDWICK: I see. Well --

MEMBER TEMPLE: Unless the responsibility for submitting them is altered.

MS. HARDWICK: Yes. We have had quite a bit of discussion exactly on that point. And that's one reason th at we do feel like we need to do some outreach with investigators in particular to explore that a bit further.

There has been the though among some Roundtable participants that yes, the investigator should bear that responsibility. And they can bear that responsibility in conjunction with dialogue with the sponsor.

But I think that's something that needs to be flushed further out. And the investigators

need to weigh in on that point.

PRESIDING OFFICER WOODCOCK: Any additional questions from the panel?

(No response.)

PRESIDING OFFICER WOODCOCK: All right, thank you very much.

MS. HARDWICK: Thank you.

PRESIDING OFFICER WOODCOCK: We will take a approximately 20 minute break. We will convene very promptly at 11 o'clock. Thank you.

(Whereupon, the above -entitled matter went off the record at 10:37 a.m. and went back on the record at 11:01 a.m.)

PRESIDING OFFICER WOODCOCK: If individuals would please take their seats, we're going to resume the proceedings. We're ready to go. Excellent.

Our next speaker will be Dr. Gary Chadwick. He's the Associate Provost at the University of Rochester. Thank you.

DR. CHADWICK: I thought this podium was set up wrong. I thought I was going to be addressing the FDA with my back to the audience. But I'm always willing to turn my backside to the FDA.

(Laughter)

DR. CHADWICK: Let me, with that remark, say that the remarks are completely my own. They don't represent the thoughts of the University. Please, no inspectors next week.

And I also wanted to start out by saying that I've been in healthcare for over 40 years. And half of that time has been directly related to improving the quality of healthcare and protecting human subjects.

And this is something that I really am very passionate a bout and care a lot about. I think most of you have my comments there. I would like to basically read through them.

Isn't that exciting? I would like to add my voice to the many that you have heard this morning and will hear the people that maintain that having IRBs review all adverse event reports is completely unworkable.

IRBs are not designed to perform this function. And dumping this Herculean task on them has undermined the IRB system to the detriment of human subjects and to science as well.

The announcement for this public hearing states that FDA would like to understand better how

IRBs' responsibility with respect to adverse events fits.

My position is that IRBs are not responsible for adverse event review and they should not be expected to conduct this review. Let me say that again.

IRBs are not responsible for adverse event review and they should not be required to conduct this review. The review of adverse events is a scientific duty, not an ethical issue.

The determination th at a study should be continued or modified, or even stopped, is the responsibility of investigators and sponsors, including the Federal agency sponsors.

It is not the IRBs' role to accomplish the adverse event review. Granted, the FDA regulations for IR B operations call for IRBs to receive reports of, quote, unanticipated problems involving risk to human subjects, unquote.

This term, however, does not equate to reviewing adverse event report forms. Most reported adverse events are anticipated or could reasonably be predicted.

And the risk they present is often unclear. In the drug regulations the FDA requires

the sponsor to notify the agency and participating investigators of adverse events associated with the use of a test article if it is, quote, both serious and unexpected, unquote.

Note that IRBs are not required to receive these reports. Unfortunately for my point of view, the device regulations state that unanticipated adverse device effects must be reported by investigators to sponsors and to the reviewing IRB.

This regulatory inconsistency has contributed to the current state of confusion about adverse event reporting. At least the term unanticipated was used in the device regulations.

But, to ensure the IRB system can work effectively, we need to get the phrase adverse events out of the IRB lexicon and off the IRBs' plate.

It's important to make three distinctions, first that reporting unanticipated problems is not the same as sending adverse event report forms.

Second, that the re gulatory term adverse events should encompass more than just eh adverse event incident form. Third, that there is a

difference between unanticipated problems and adverse events.

There are vastly many more adverse events in research than there are truly unanticipated problems. To do their job, IRBs need to focus on the unanticipated problems and not on adverse event reports.

As the announcement for this hearing and the FDA regulations sate, IRBs are responsible for conducting continuing review of resea rch at intervals appropriate to the risks.

This periodic review is a snapshot of a study at points along the progress, that is, whenever change is requested or the study approval is extended, usually once per year.

So, by regulation, IRBs must conduct continuing review. But they were never intended to conduct continuous monitoring. Adverse event monitoring requires continuous monitoring and should be accomplished by sponsors and investigators.

Guidance documents and FDA regulations, particularly regulatory devices, are partially responsible for the unworkable adverse event review situation that exists today.

The requirement for reporting unanticipated problems has never been clear under either the FDA or the HHS regulations. And IRBs, sponsors, and investigators have struggled with its meaning for years.

I believe that the term reports of unanticipated problems was intended to mean summary reports with analysis and conclusions about the unanticipated problem and corrections to resolve the issue, not just simple reports of an occurrence which may or may not have been predictable.

Mis-application, mis -interpretation, and/or misunderstanding of the regulations have caused adverse event report forms to jam into the void created by the lack of under standing about the reporting requirement for unanticipated problems.

Even Federal agencies seem to be confused. Despite having no regulatory basis, current HHS guidance on continuing review states, quote, continuing review of research by the IRB should include consideration of adverse events, unquote.

And it says even when a data safety monitoring board is in place, quote, the IRB still must receive and review reports of local on -site

adverse events, unquote.

Fear is driving the system to be over - inclusive. No one wants to be out of compliance. So, instead of considerate and useful summary reports from our own investigators, IRB has received stacks of duplicative raw data in hundreds of varying formats from dozens of sources.

To make matters worse , investigators are inclined merely to pass these raw report forms onto the IRB without any thought as to their meaning or providing any expert opinion to the IRB.

Reviewing reams of adverse event reports is not a task for which IRBs are equipped. This futile activity as added to the workload of IRBs, drained their limited resources, and blurred the essential role that they play in human subject protection.

Removing the responsibility for adverse event reviews would go a long way toward allowing IRBs to maintain focus on their central mission of ethical review and improvement of human subject protection.

It is within the FDA's power to rectify the current situation by clearly stating that submission of all adverse event report forms to

IRBs is neither required nor desired.

This remedy could be quickly accomplished through guidance issued by the FDA, preferably jointly with HHS. The announcement asked that we address questions posed in three areas.

The first, what role should IRBs play in the review of adverse events information? It's my view, as you can see, that IRBs should play no role in the routine review of adverse event reports.

IRBs are not scientific review committees. IRBs are not data safety monitoring boards. There are limitations o n the IRB review and committee makeup that make the review of adverse events an activity essentially devoid of utility, including the fact that IRBs receive reports from investigators who often do not know in which arm the adverse event occurred, the numbe rs of events, the numbers of subjects, and other details critical for taking any reasonable action.

If these meaningless reports are sent to the IRB, however, someone has to do something with them. Thus, IRB resources are expended on reviews with little or not benefit to human subject protection.

Adverse event reports should not be sent

to the IRB at all, period. To clarify the review and analysis of adverse event reports should occur, just not by the IRB.

It doesn't make sense to have adverse events reviewed by a committee of bankers, clergy, psychologists and social workers. It's time for the FDA to codify its guidance on the use of data monitoring committees as a subject protection mechanism in clinical trials.

If FDA were to require safety mon itoring plans and require data monitoring committees in clinical trials, then the IRB could focus on its required role under the regulations and review the plan for monitoring and approve its adequacy for the particular study at hand.

Part of that plan s hould be description of the types of events that will be reported as unanticipated problems. The review of the investigator safety monitoring plan is an appropriate activity for IRBs.

And it helps to ensure that the review of safety reports is accomplis hed in an effective and timely manner by appropriately trained and qualified people.

Question two, IRBs are routinely saddled

with the review of any adverse event report that comes in the front door. Any and all adverse events are reported, not just tho se meeting the criteria of serious unexpected and related as required by the FDA regulations.

Several research institutions, Penn and ours, and others, have attempted to limit the reporting to only those events meeting the FDA criteria, that is only even ts that are probably or definitely related and unexpected and serious are to be reported.

Often these institutional policies don't work very well because sponsors and federally funded research bases, especially in AIDS and oncology, send all kinds of rep orts to their investigators and insist they send them to the IRB, and threaten to put investigators out of compliance if they don't get some acknowledgement of review from the IRB.

Again, fear, not efficiency or effectiveness, is driving the system. To stop the drain on IRB resources, the flow must stop. Should IRB responsibilities for multi -site trials differ from those for single site trials?

As this question implies, multi -site

studies are different from single -site studies in important ways, inclu ding the locus of responsibility for protocol design and the oversight of the study.

The most useless information for IRBs comes from multi-site studies, raw data on multiple adverse event reports from multiple sources. Reviewing this report is akin to finding a needle in a haystack while blindfolded and wearing gloves.

IRBs are dedicated people. And they struggle. And, on rare occasions, they have found needles in a haystack. But it's counterproductive to insist that valuable IRB time be devoted to this nearly fruitless activity.

The same time spent in more productive ways would have much greater positive benefit on study conduct, human safety, and fostering cooperative relationships between the IRB and investigators.

IRBs must be allowed to get out of the business of routinely reviewing adverse event reports, regardless of where they occurred. In 1999, in response to a Congressional directive to reduce unnecessary burdens, the NIH issued guidance instructing data safety monitoring boards on NIH

sponsored multi -site trials to forward summary reports of adverse events to each IRB involved in the study.

This policy allows processed information from a single source to be considered by the IRB. This is a reasonable approach for a multi -site and even single site studies with such monitoring committees.

Routinely, however, NIH -funded research bases violate their own policy and send pages and pages of separate report forms to investigators for forwarding to their IRBs, unprocessed, unrelated, useless points of data.

For single site studies, the institution and its investigators bear the full responsibility for scientific and subject safety monitoring. An effective system for appropriate study monitoring is an absolute requirement for ethical research.

But it is not, and should not be, the job of the IRB to do that. Instead of developing appropriate structures and devoting the additional resources, institutions have tended to dump tasks and responsibilities on the IRB because of their easy availab ility, to use a phrase from the Belmont's Report description of unjust practices.

And, because the tendency is to see the IRB as the only responsible party for human subject protection, it is not. IRBs' cannot do it all. While the FDA cannot control in ternal institutional behavior to the extent that vital human subject protections and regulatory protections are compromised by these additional burdens, it is a problem for the FDA and the studies they regulate.

What types of adverse events should the IRB receive? As I stated previously, IRBs should not routinely review adverse event reports. Adverse event report forms generally do not provide information that IRBs can use effectively.

And they should not be submitted to IRBs. A summary analysis based upon an event that is, one, related to the study, two, serious, and three, truly unexpected, can provide some useful data.

But, even then, it's the analysis of the investigator and/or the monitoring committee that is essential to turn the data into info rmation, the point that a previous speaker has made.

Are there circumstances under which the IRB should receive information about adverse events that are not both serious and unexpected? The IRB should receive an adverse event summary whenever it

supports a study change, for example, temporary suspension, termination, change in protocol, consent, change in recruitment, and so forth, and when studies are continued in the face of truly unanticipated problems.

But, again, the adverse event report should be stapled to the back of the request for the change. An adverse event that is either serious or unexpected might provide part of the justification for that change, depending on the investigator or sponsor assessment.

As part of the continuing review process, IRBs must reassess the risks of the study. Summary information about the actual adverse event experience is important in that process.

But, submitting individual forms or tabular data alone is not very helpful. It's the analysis that is useful. Should the criteria for reporting adverse events differ depending on whether adverse events occur at the IRB site or another site?

The typical adverse event report form does not provide the IRB with useful information, even if the event occurred locally. What is useful is the analysis that includes what happened, why

the investigator thought it happened, and what actions are necessary in light of the occurrence.

In a multi -site study, the adverse event report form should be forwarded to the sponsor or the study monitoring committee for an aggregated analysis with other site report forms.

And only the summary of that analysis should be reported back to the reviewing IRBs. For local events that are related and serious, and truly unexpected, the local i nvestigator should provide a summary and analysis based on the information available.

The standard for all studies should be that the IRB receive summary information to support actions, not individual adverse event report forms. We need information, not data.

The FDA's announcement states that there seems to be a general consensus in the IRB community that adverse event reports submitted individually and sporadically throughout the course of the study without any type of interpretation are ordinarily not informative to permit IRBs to assess implications for study subjects.

I agree with this consensus statement. As a remedy, IRB should not be expected nor

required to receive adverse event reports. As this question implies, it is the information from t he events that is useful.

And that's what needs to be provided. Report forms should be available for audit, further analysis, and for study documentation. But the IRB should not routinely receive them.

Again, IRBs are not scientific review committees. Sponsors and investigators have those -- or should have those. All IRBs are required to have some members who have non-scientific and non-technical backgrounds.

Consolidated reports and individual summary reports should be in narrative format and written in plain language. Only consolidated reports should be included as part of the IRB submission for continuing review.

Additionally, when a change in the study is requested based upon adverse events, a summary of the events should accompany the reque st. If the investigator or the sponsor suspends a study because of adverse events, which is their responsibility, a brief statement of the facts should be presented to the IRB with notification of the suspension with a more detailed analysis and

recommendation to follow.

Who should provide such reports? For single site studies, the investigator is responsible for conducting and reporting this analysis.

If the investigator's study monitoring plan indicates that there is a data monitoring committee, then that body should supply the summary report.

For multiple site studies, or multi - center studies, the study's sponsor or research base should provide that information, preferably, again, through a data monitoring committee.

Should the approach be the s ame for drugs and devices? Yes, absolutely. A major source of frustration for IRBs is the different agency regulations require different responses.

Even worse, different offices within the same agency interpret requirements differently. Guidance docum ents provide conflicting advice. Standardization of guidance would be a definite improvement and would help promote consistency across research institutions and improve the protection for research subjects.

To conclude, I wish to restate that

reporting unanticipated problems is not the same as sending in adverse event report forms. FDA and HHS could correct the confusion of terms, fix the unrealistic expectations, and remedy the situation by issuing clear guidance to sponsors, investigators, institution s, and IRBs that makes the following points.

One, submitting adverse event report forms to the IRB does not satisfy the FDA's requirement for adverse event reporting. Reports are to be submitted to and analyzed by sponsors and sponsor investigators.

Two, reports of unanticipated problems, not adverse event reports, to the IRB must include an analysis of the events and recommended actions. Adverse event reporting forms sent to IRBs without accompanying analysis should be returned if original or destroye d if copies without any acknowledgement, review, or comment required.

Institutions conducting human subject research and sponsors should put in place and support systems for the ongoing monitoring of studies, for example, data monitoring committees for clinical trials.

And, five, IRBs are not expected to

provide continuous monitoring, beyond what is required in the continuing review requirements of the current regulations.

Because of concern that other parties may not adequately perform this responsib ility, it may be hard for some IRBs to lay down this assumed or imposed burden.

Investigators in research institutions may resist establishing and supporting effective systems for monitoring. It may be even difficult for the FDA to redirect adverse eve nt reviews away from IRBs.

But, unless all this is done, the IRB system will struggle and ultimately fail. I thank you for your interest in resolving this complex and important issue, and for the opportunity to provide some input.

PRESIDING OFFICER WO ODCOCK: Thank you very much. Do we have questions from the panel? Dr. Schwetz?

MEMBER SCHWETZ: Gary, of the protection that happens today, from the reading of adverse event reports either by IRBs, investigators, or sponsors, what portion of that prote ction do you think occurs because IRB members read it, as